

## TENT COOPERATION TREATY (

IFD

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:  
WOLF, GREENFIELD & SACKS, P.C.  
Attn. LOCKHART, HELEN C.  
600 Atlantic Avenue  
Federal Reserve Plaza  
Boston, Massachusetts 02210  
UNITED STATES OF AMERICA

REGISTERED

## INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

Applicant's or agent's file reference <b>M0656/7046W0</b>	Date of mailing (day/month/year) <b>01/02/2000</b>
International application No. <b>PCT/US 99/ 19841</b>	International filing date (day/month/year) <b>27/08/1999</b>
Applicant <b>MASSACHUSETTS INSTITUTE OF TECHNOLOGY</b>	

## 1. This International Searching Authority

- (i) considers that there are 2 (number of) inventions claimed in the international application covered by the claims indicated ~~below~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~ on the extra sheet:

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FEB 11 2000

File Folder	4-1-00	<input checked="" type="checkbox"/>	Initials
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Docket Entry	3-1700	<input checked="" type="checkbox"/>	
Docket Cross Off		<input type="checkbox"/>	
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Annuities		<input type="checkbox"/>	
Confirmation		<input type="checkbox"/>	

- (ii) ☒ has carried out a partial international search (see Annex) ☐ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:  
**1-21, 31, 46-57(comp1.), 30, 33-45 (partly)**
- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **Invited**, within the time limit indicated above, to pay the amount indicated below:

EUR 945,00 x 1 = EUR 945,00  
Fee per additional invention      number of additional inventions      total amount of additional fees

Or, \_\_\_\_\_ x \_\_\_\_\_ = \_\_\_\_\_

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☒ Claim(s) Nos. see remark have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority



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Authorized officer

Mireille Claudepierre

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-21,31,46-57 (all completely), 30, 33-45 (all partly)

A modified heparinase II, pharmaceutical preparation comprising it, method of cleaving a glycosaminoglycan with said heparinase II, nucleic acid encoding it, end vector and host cell comprising said nucleic acid.

2. Claims: 22-29, 32 (all completely), 30, 33-45 (all partly)

A modified heparinase I having enzymatic activity that is not dependent on the presence of calcium, pharmaceutical preparation comprising said heparinase I, method of cleaving a glycosaminoglycan employing said heparinase I

#### MOTIVATION:

The closest prior art with respect to the present patent application is represented by The Journal of Biological Chemistry 273, pages 10160-10167 and Biochemistry 34, pages 14441-14448. The first document discloses heparinase II mutants with reduced enzymic activity toward heparin and/or heparan sulfate (see Table I), the latter document discloses heparinase I mutants also with reduced activity (see Table 3).

In the light of this prior art, the problem underlying the present application is the provision of further heparinase mutants with reduced activity, for use as a therapeutic agent. The solutions to this problem disclosed and claimed in the present application consists of a modified heparinase II with a modified product profile and a modified heparinase I having enzymatic activity that is not dependent on the presence of calcium.

Due to the fact that modified heparinases are known, and due to the essential differences in primary structure of heparinase II and heparinase I, and due to the fact that no other technical features can be distinguished which, in the light of the prior art could be regarded as special technical features in the sense of Rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently there is lack of unity and the different inventions, are formulated as the different subjects mentioned above.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206**

Continuation of Box 3.

Although claims 35-44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the heparinase.

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1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:

see 'Invitation to pay additional fees'

2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 34635 A (IBEX TECHNOLOGIES ;ZIMMERMANN JOSEPH (US)) 21 December 1995 (1995-12-21) page 32, line 1 - line 6; example 7 ---	1-21, 30, 31, 33, 34, 46-57
X	SHRIVER Z ET AL.: "Heparinase II from flavobacterium heparinum: Role of histidine residues in enzymatic activity as probed by chemical modification and site-directed mutagenesis" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 17, 24 April 1998 (1998-04-24), pages 10160-10167, XP002127285 MD US table I ---	1-5, 7-13, 16, 17, 19-21, 30, 31, 33, 34, 46-52
A	SASISEKHARAN R ET AL: "HEPARINASE I FROM FLAVOBACTERIUM HEPARINUM: THE ROLE OF THE CYSTEINE RESIDUE IN CATALYSIS AS PROBED BY CHEMICAL MODIFICATION AND SITE-DIRECTED MUTAGENESIS" BIOCHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, PA, vol. 34, no. 44, page 14441-14448 XP002026383 ISSN: 0006-2960 cited in the application the whole document ---	1-21

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

**Annex to Form PCT/ISA/206**  
**COMMUNICATION RELATING TO THE RESULTS**  
**OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No  
 US 99/19841

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>SHRIVER Z ET AL.: "Heparinase II from            Flavobacterium heparinum: Role of cysteine            in enzymatic activity as probed by            chemical modification and site-directed            mutagenesis"            JOURNAL OF BIOLOGICAL CHEMISTRY, -            vol. 273, no. 36,            4 September 1998 (1998-09-04), pages            22904-22912, XP002127286            MD US            the whole document            -----</p>	<p>1-21,30,            31,33,            34,46-52</p>

# Patent Family Annex

Information on patent family members

International Application No

/US 99/19841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9534635 A	21-12-1995	US 5681733 A	28-10-1997
		AU 694241 B	16-07-1998
		AU 2771095 A	05-01-1996
		CA 2192159 A	21-12-1995
		EP 0763101 A	19-03-1997
		JP 10511841 T	17-11-1998
		US 5919693 A	06-07-1999
		ZA 9504781 A	08-02-1996
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